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Brief Report

Glucocorticoids for treating paediatric pulmonary hypertension: a novel use for a common medication

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Abstract Laboratory investigations have shown the role of inflammation in the pathogenesis of pulmonary hypertension and improvement after anti-inflammatory drugs. Despite these observations, reports on the use of steroids to treat pulmonary hypertension in humans are absent from the literature. In this article, we report the use of glucocorticoids in the treatment of two children with pulmonary hypertension, demonstrating its potential utility.

Keywords: Pulmonary hypertension; inflammation; glucocorticoids

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Pulmonary hypertension in children is a devastating diagnosis with significant morbidity and mortality. Causes for pulmonary hypertension in children include idiopathic pulmonary arteriolar dysfunction, CHD, and chronic lung disease, especially in premature infants.[1] Robust laboratory investigations have shown that inflammation disrupts multiple molecular pathways leading to pulmonary hypertension. Inflammatory cell lines and elevated pro-inflammatory cytokines have been identified in tissue and sera from patients with pulmonary hypertension.[2] In rats, dexamethasone has been shown to attenuate the development of pulmonary hypertension and even reverse the pathology.[3,4] Human smooth muscle cell growth is inhibited by prednisolone in vitro.[5] Despite the literature on anti-inflammatory medications in treatment of pulmonary hypertension, limited literature exists on treating pulmonary hypertension with anti-inflammatory medications in humans. In this article, we present the cases of two children with severe pulmonary hypertension that improved when treated with glucocorticoids.

Patient one was a former 31-week-gestation infant with an uncomplicated intensive care course who presented at 6 months of age to an outside hospital with respiratory distress and hypoxia. Support was rapidly escalated with intubation, muscle paralysis, and multiple inotropes. All viral and bacterial cultures were negative. An echocardiogram showed suprasystemic right heart pressures (tricuspid regurgitation jet derived pressure 106 mmHg, systolic blood pressure 60 mmHg, and paradoxical ventricular septal motion with "pancaked" left ventricle), and she was transferred for a lung transplant evaluation. A cardiac catheterisation performed while mechanically ventilated, muscle relaxed, and on 100% oxygen, 20 ppm of inhaled nitrous oxide, oral sildenafil, dopamine, and epinephrine demonstrated suprasystemic right ventricular pressures (right ventricular systolic pressure 103 mmHg, left ventricular systolic pressure 57 mmHg, indexed pulmonary vascular resistance of 25.7 Wood units $\times$ m^2). Intravenous epoprostenol was subsequently initiated. Over the next 3 days, the child's clinical condition continued to deteriorate with worsening spells of hypoxia and hypotension. Within 48 hours of initiating methylprednisolone at 2 mg/kg/day, the child's clinical course improved significantly with no further spells and a reduction in inotropic support and oxygen. An open lung biopsy found non-specific features of diffuse medial hypertrophy, normal venules and capillaries, and rare lymphocytes. After 11 days, she was weaned off steroids with improved right ventricular function and septal position though an insufficient tricuspid regurgitation jet on

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echocardiograms. The child was transferred out of the ICU on supplemental oxygen, increased dose of epoprostenol, and sildenafil. The child developed worsening respiratory distress and hypoxia 10 days after stopping steroids. Oral prednisone 2 mg/kg/day was again initiated and with notable clinical improvement within 36 hours. The child was discharged home, and steroids were successfully weaned over a 3-month period. The child continues to thrive, and has been weaned off all pulmonary vasodilators in the 9 years since treatment.

Patient two had Trisomy 21, and was initially seen at 1 month of age with a moderate-sized, atrial-level defect, no ventricular septal defect, and evidence of suprasystemic right heart pressures with a pancaked left ventricle. Cardiac catheterisation at 3 months of age showed systemic right ventricular pressures (mean pulmonary arterial pressure 44 mmHg, indexed pulmonary vascular resistance 4.7 Woods units $\times$ m^2) with minimal responsiveness to inhaled nitric oxide. At 5 months of age, the atrial defect was surgically closed without complications, and he was discharged home on sildenafil. Follow-up at 8 months of age, however, showed pancaked interventricular septum and suprasystemic pulmonary pressures (tricuspid valve regurgitation jet derived pressure of 70 mmHg), and the child clinically had poor feeding and diaphoresis. A 5-day burst of prednisone at 2 mg/kg/day improved clinical symptoms. The child was admitted 2 months later to the ICU with right heart failure, and an echocardiogram showed suprasystemic right heart pressures (tricuspid regurgitation jet 75 mmHg) with decreased right ventricular systolic function. He was initiated on nasal cannula-inhaled nitric oxide, milrinone, and furosemide on admission. The next day, bosentan and intravenous methylprednisone at 4 mg/kg/day were added. Within 72 hours of steroid initiation, milrinone and inhaled nitric oxide were weaned off, and an echocardiogram showed right ventricular pressures that were half systemic (tricuspid regurgitation jet 40 mmHg). The child was discharged home on sildenafil, furosemide, bosentan, and a 2.5-month prednisolone taper. Now at 6 years of age, he is maintained on sildenafil and ambrisentan with no further admissions.

Discussion

The role of inflammatory cell lines and cytokines in the pathogenesis of pulmonary arterial hypertension as well as steroid-induced improvement in clinical and laboratory indicators in animal models has been well described in the literature.[2] Given this compelling evidence and the low side-effect profile of steroids, why are there no studies examining the possible benefits of glucocorticoids in treating people with pulmonary hypertension? Outside of patients with pulmonary hypertension secondary to sarcoidosis, there is only a single case report of an adult female with idiopathic pulmonary hypertension who showed marked improvement in her pulmonary hypertension after treatment with prednisolone for idiopathic thrombocytopaenic purpura.[6] We have found no studies suggesting its usefulness in children.

Our two cases demonstrate what we feel is a relatively clear cause and effect regarding the benefit of glucocorticoids in treating children with pulmonary hypertension. In addition to these two children, we have treated a number of others cases that we feel improved with steroid therapy. Simultaneous treatments make the argument for the specific role of glucocorticoids more difficult; nonetheless, we felt that children who respond best to steroids were usually less than 2 years of age, and often with a diagnosis other than idiopathic pulmonary hypertension. Interestingly, diseases with some degree of alveolar hypoplasia seemed particularly responsive including bronchopulmonary dysplasia, congenital diaphragmatic hernia, giant omphalocele, and trisomy 21. Our current practice is to initiate a 5–7-day steroid burst of either prednisone or methylprednisone at 2 mg/kg/day (up to 4 mg/kg/day), a dose comparable with treatment regimens for children with reactive airway disease. If there is no clinical or echocardiographic improvement in pulmonary hypertension, we stop the steroids. If there is improvement, we begin a taper of 0.5 mg/kg/week with the total treatment period lasting about a month. Near the end of the treatment period, we re-assess for rebound pulmonary hypertension. Oftentimes, other pulmonary hypertensive medications such as sildenafil were utilised concomitantly. Occasionally, we have found it helpful to extend treatment courses, utilising every other day dosing or intermittent bursts in hopes of avoiding long-term side-effects. We have not seen any adverse complications secondary to use of steroids in these children.

Inflammation plays an unequivocal role in the pathogenesis of pulmonary hypertension based on laboratory and animal data; furthermore, our clinical observations suggest that modulating inflammation using glucocorticoids may benefit children with pulmonary hypertension. Thus, given the unequivocal role inflammation plays in pulmonary hypertension based on laboratory and animal data as well as our observations, we advocate for controlled clinical trials to assess the potential effectiveness of steroids in treating pulmonary hypertension in children. A similar view has been suggested for treatment of adults with pulmonary hypertension.[7] Proof of their utility could have significant implications for child health, given the ready availability of glucocorticoids, their immense affordability compared with other pulmonary hypertension medications, and their relatively low side-effect profile.

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Conflicts of Interest

None.

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